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A61K 311K



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Office européen des brevets

0070 714
A1

EUROPEAN PATENT APPLICATION

(19)

(11)

Publication number:

(12)

(21)

Application number: 82303756.9

(51)

Int. Cl.²: C 07 C 57/30, C 07 C 57/58,
A 61 K 31/19

(22)

Date of filing: 16.07.82

(30)

Priority: 20.07.81 US 284414
20.07.81 US 284656

(71)

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Date of publication of application: 26.01.83
Bulletin 83/4

(72)

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Designated Contracting States: BE CH DE FR GB IT LI
NL SE

(74)

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(54)

Method and composition for treating respiratory disorders.

(57)

A process for treating adult respiratory distress syn-
drome comprises the systemic administration of ibuprofen or
flurbiprofen or a salt or ester thereof. Dosage forms are also
disclosed.

EP 0 070 714 A1

UPJOHN

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GJE 6182/59

METHOD AND COMPOSITION FOR TREATING RESPIRATORY DISORDERS

This invention relates to a method and a composition for treating respiratory disorders, in particular adult respiratory distress syndrome.

Ibuprofen, its salts and esters, are known to be useful for treating a variety of medical conditions, including inflammation, arthritis and dental pain, for reducing platelet adhesiveness and in coronary infarct. Flurbiprofen, another non-steroidal anti-inflammatory drug, has been used in rheumatic and degenerative diseases of the joints and for reducing platelet adhesiveness.

"Shock lung", now known as the adult respiratory distress syndrome (ARDS), generally occurs following massive trauma; there are, however, many other causes. The etiologies of this syndrome, its clinical aspects and means of preventing and treating it, are disclosed by Dr. Roger C. Bone, M.D. in "Diagnosis and Management of Adult Respiratory Distress Syndrome"; Practical Cardiology, Vol. 5, No. 2, pp. 49-63, February, 1979. Dr Bone discloses medicinal treatments with antibiotics, cortico-steroids and antacids.

It has now been discovered that ibuprofen (p-isobutyl-hydratropic acid) and flurbiprofen (3-fluoro-4-phenylhydrotropic acid), their C₁₋₈ alkyl esters and their pharmacologically acceptable salts, are of utility in treating ARDS.

Examples of the esters are the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and octyl esters. Examples of the pharmacologically acceptable salts are the alkali metal, alkaline earth and ammonium salts.

Compounds or compositions (including a pharmaceutically acceptable carrier) for use in the present invention can be presented for systemic administration to humans and animals, e.g. in unit dosage forms such as tablets, capsules or pills, or as powders, granules, suppositories, sterile parenteral solutions or suspensions, sterile non-parenteral solutions or suspensions, or oral solutions or suspensions, containing suitable quantities of an active ingredient.

For oral administration either solid or fluid unit dosage forms can be prepared.

5 Powders are prepared quite simply by comminuting the active ingredient to a suitably fine size and mixing with a similarly comminuted diluent. The diluent can be an edible carbohydrate material such as lactose or starch. Advantageously, a sweetening agent or sugar is present as well as a flavoring oil.

10 Capsules are produced by preparing a powder mixture as herein-after described and filling into formed gelatin sheaths. Advantageously, as an adjuvant to the filling operation, a lubricant such as talc, magnesium stearate, calcium stearate and the like is added to the powder mixture before the filling operation.

15 Soft gelatin capsules are prepared by machine encapsulation of a slurry of active ingredients with an acceptable vegetable oil, light liquid petrolatum or other inert oil or triglyceride.

20 Tablets are made by preparing a powder mixture, granulating or slugging, adding a lubricant and pressing into tablets. The powder mixture is prepared by mixing an active ingredient, suitably comminuted, with a diluent or base such as starch, lactose, kaolin, dicalcium phosphate and the like. The powder mixture can be granulated by wetting with a binder such as corn syrup, gelating solution, methylcellulose solution or acacia mucilage and forcing through a screen. As an alternative to granulating, the powder mixture can be slugged, i.e., run through the tablet machine and the resulting imperfectly
25 formed tablets broken into pieces (slugs). The slugs can be lubricated to prevent sticking to the tablet-forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets.

30 Advantageously, the tablet can be provided with a protective coating consisting of a sealing coat or enteric coat of shellac, a coating of sugar and methylcellulose and a polish coating of carnauba wax.

35 Fluid unit dosage forms for oral administration such as syrups, elixirs and suspensions can be prepared wherein each teaspoonful of composition contains a predetermined amount of active ingredient for administration. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic

vehicle with suitable sweeteners together with a flavoring agent. Suspensions can be prepared of the insoluble forms with a suitable vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

5 For parenteral administration, fluid unit dosage forms are prepared utilizing an active ingredient and a sterile vehicle, water being preferred. The active ingredient, depending on the form and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the water-soluble active ingredient can be dis-
10 solved in water for injection and filter sterilized before filling into a suitable vial or ampule and sealing. Advantageously, adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. Parenteral suspensions are prepared in substantially the same manner except that an active ingredient is
15 suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The active ingredient can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the
20 active ingredient.

In addition to oral and parenteral administration, the rectal and vaginal routes can be utilized. An active ingredient can be administered by means of a suppository. A vehicle which has a melting
25 point at about body temperature or one that is readily soluble can be utilized. For example, cocoa butter and various polyethylene glycols (carbowaxes) can serve as the vehicle.

The term "unit dosage form" as used in the specification and claims refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined
30 quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the novel unit dosage forms of this invention are dictated by and are directly dependent on
35 (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitation inherent in the art of compounding such an active material for therapeutic use in humans, as disclosed in this specification, these being features of the present invention. Examples of suitable unit dosage forms in ac-

cord with this invention are tablets, capsules, troches, suppositories, powder packets, wafers, cachets teaspoonfuls, tablespoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing, and other forms as herein described.

5 The systemic administration of ibuprofen or flurbiprofen or a salt or ester thereof, to humans provides a useful method of treating ARDS and a means for reducing non-cardiac pulmonary edema and non-cardiac pulmonary hypertension.

10 The dose of ibuprofen, its salts or esters, for treating ARDS is the same dose known for treating conditions for which it is previously known to be useful. In general, from about 2.5 mg to about 50 mg per kilogram body weight administered daily in single or divided dosage amount.

15 The dose of flurbiprofen, its salts or esters, for treating ARDS is the same dose known for treating conditions for which it is previously known to be useful. In general, from about 0.25 mg to about 5.0 mg per kilogram body weight administered daily in single or divided dosage amount or an adult daily does of up to 300 mg/day in divided dose.

20 The following examples are illustrative of the present invention, but are not intended to be limiting.

Example 1 Hard Gelatin Capsules

25 One thousand two-piece hard gelatin capsules for oral use, each capsule containing 100 mg of ibuprofen are prepared from the following types and amounts of ingredients:

Ibuprofen	100 gm
Lactose	100 gm
Corn starch	20 gm
Talc	20 gm
30 Magnesium stearate	2 gm

 The ibuprofen finely divided by means of an air micronizer, is added to the other finely powdered ingredients, mixed thoroughly and then encapsulated in the usual manner.

35 The foregoing capsules are useful for treating ARDS by the oral administration of two capsules four times a day.

 Using the procedure above, capsules are similarly prepared containing ibuprofen in 300, 400, and 600 mg amounts by substituting 300, 400, and 600 gm of ibuprofen for the 100 gm used above.

Example 2 Soft Gelatin Capsules

One-piece soft gelatin capsules for oral use, each containing 300 mg of ibuprofen (finely divided by means of an air micronizer) are prepared by first suspending the compound in 0.5 ml of corn oil to render the material capsulatable and then capsulating in the above manner.

The foregoing capsules are useful for treating ARDS by the oral administration of two capsules four times a day.

Example 3 Tablets

One thousand tablets, each containing 300 mg of ibuprofen are prepared from the following types and amounts of ingredients:

	Ibuprofen micronized	300 gm
	Lactose	75 gm
	Corn starch	50 gm
15	Magnesium stearate	4 gm
	Light liquid petrolatum	5 gm

The ibuprofen (finely divided by means of an air micronizer) is added to the other ingredients and then thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each tablet containing 300 mg of ibuprofen.

The foregoing tablets are useful for treating ARDS by the oral administration of one or two tablets four times a day.

Using the procedure above, tablets are similarly prepared containing ibuprofen in 400 mg and 600 mg amounts by substituting 400 gm and 600 gm of ibuprofen for the 300 gm used above.

Example 4 Oral Suspension

One thousand ml of an aqueous suspension for oral use, containing in each teaspoonful (5 ml) dose, 100 mg of ibuprofen, aluminum salt is prepared from the following types and amounts of ingredients:

	Ibuprofen, Aluminum Salt	
	micronized	20 gm
	Citric acid	2 gm
	Benzoic acid	1 gm
35	Sucrose	700 gm
	Tragacanth	5 gm
	Lemon oil	2 gm
	Deionized water, q.s.	1000 ml

The citric acid, benzoic acid, sucrose, tragacanth and lemon oil are dispersed in sufficient water to make 850 ml of suspension. The ibuprofen aluminum salt (finely divided by means of an air micronizer) is stirred into the syrup until uniformly distributed. Sufficient water is added to make 1000 ml.

The composition so prepared is useful for treating ARDS at a dose of one tablespoonful (15 ml) four times a day.

Example 5

A sterile aqueous solution for parenteral (i.v.) injection, containing in one liter, 350 mg of ibuprofen, sodium salt is prepared from the following types and amounts of ingredients:

Ibuprofen sodium salt 350 mg

Water for injection, q.s. 1000 ml

To the sterile solution is added sterilized ibuprofen, sodium salt and filled into sterile containers sealed.

The composition so prepared is useful for treating ARDS at a dose of one liter every eight hours.

Example 6 Hard Gelatin Capsules

One thousand two-piece hard gelatin capsules for oral use, each capsule containing 50 mg of flurbiprofen are prepared from the following types and amounts of ingredients:

flurbiprofen 50 gm

Lactose 100 gm

Corn starch 20 gm

Talc 20 gm

Magnesium stearate 2 gm

The flurbiprofen finely divided by means of an air micronizer, is added to the other finely powdered ingredients, mixed thoroughly and then encapsulated in the usual manner.

The foregoing capsules are useful for treating ARDS by the oral administration of one capsule four times a day.

Using the procedure above, capsules are similarly prepared containing flurbiprofen in 25, 75, and 100 mg amounts by substituting 25, 75, and 100 gm of flurbiprofen for the 50 gm used above.

Example 7 Soft Gelatin Capsules

One-piece soft gelatin capsules for oral use, each containing 25 mg of flurbiprofen (finely divided by means of an air micronizer) are prepared by first suspending the compound in 0.5 ml of corn oil to

render the material capsulatable and then capsulating in the above manner.

The foregoing capsules are useful for treating ARDS by the oral administration of two capsules four times a day.

5 Example 8 Tablets

One thousand tablets, each containing 100 mg of flurbiprofen are prepared from the following types and amounts of ingredients:

	flurbiprofen micronized	100 gm
	Lactose	75 gm
10	Corn starch	50 gm
	Magnesium stearate	4 gm
	Light liquid petrolatum	5 gm

The flurbiprofen (finely divided by means of an air micronizer) is added to the other ingredients and then thoroughly mixed and
15 slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each tablet containing 100 mg of flurbiprofen.

The foregoing tablets are useful for treating ARDS by the oral administration of one tablet three times a day.

20 Using the procedure above, tablets are similarly prepared containing flurbiprofen in 25 mg and 50 mg amounts by substituting 25 gm and 50 gm of flurbiprofen for the 100 gm used above.

Example 9 Oral Suspension

25 One thousand ml of an aqueous suspension for oral use, containing in each teaspoonful (5 ml) dose, 100 mg of flurbiprofen, aluminum salt is prepared from the following types and amounts of ingredients:

	flurbiprofen, Aluminum Salt	
	micronized	20 gm
	Citric acid	2 gm
30	Benzoic acid	1 gm
	Sucrose	700 gm
	Tragacanth	5 gm
	Lemon oil	2 gm
	Deionized water, q.s.	1000 ml

35 The citric acid, benzoic acid, sucrose, tragacanth and lemon oil are dispersed in sufficient water to make 850 ml of suspension. The flurbiprofen aluminum salt (finely divided by means of an air micronizer) is stirred into the syrup until uniformly distributed. Suf-

ficient water is added to make 1000 ml.

The composition so prepared is useful for treating ARDS at a dose of one teaspoonful (5 ml) three times a day.

Example 10

- 5 A sterile aqueous solution for parenteral (i.v.) injection, containing in one liter, 150 mg of flurbiprofen, sodium salt is prepared from the following types and amounts of ingredients:

flurbiprofen sodium salt 150 mg

Water for injection, q.s. 1000 ml

- 10 To the sterile solution is added sterilized flurbiprofen, sodium salt and filled into sterile containers sealed.

The composition so prepared is useful for treating ARDS at a dose of one liter every twelve hours.

Example 11

- 15 Following the procedure of the proceeding Examples 1 through 10, inclusive, compositions are similarly prepared substituting equimolar amounts of the ester, e.g., methyl, ethyl, isopropyl, octyl, or salt, e.g., sodium, potassium, ammonium, for the compound of the examples.

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CLAIMS

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1 A process for treating adult respiratory distress syndrome com-
2 prising the systemic administration to a human or animal of an ef-
3 fective amount of p-isobutylhydratropic acid or 3-fluoro-4-phenyl-
4 hydratropic acid or an alkyl ester of from 1 to 8 carbon atoms, in-
5 clusive, including isomeric forms thereof, or a pharmacologically
6 acceptable salt thereof.

-2-

1 The process of Claim 1 wherein the compound is p-
2 isobutylhydratropic acid.

-3-

1 The process of Claim 1 wherein the compound is 3-fluoro-4-
2 phenylhydratropic acid.

-4-

1 A composition for use to treat adult respiratory distress syn-
2 drome comprising, in unit dosage form, an effective amount of p-
3 isobutylhydratropic acid or 3-fluoro-4-phenylhydratropic acid or an
4 alkyl ester of from 1 to 8 carbon atoms, inclusive, including isomeric
5 forms thereof or a pharmacologically acceptable salt thereof, in com-
6 bination with a pharmaceutical carrier. X

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PARTIAL EUROPEAN SEARCH REPORT
 which under Rule 45 of the European Patent Convention
 shall be considered, for the purposes of subsequent
 proceedings, as the European search report

Application number

EP 82 30 3756

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 7)
X	GB - A - 1 527 563 (UPJOHN CO) * Claims 1,9-15 * --	4	C 07 C 57/30 57/58 A 61 K 31/19
X	CHEMICAL ABSTRACTS, Vol. 93, no. 11, September 15, 1980, page 78, ref. 107260g Columbus, Ohio, US B.I. JUGDUTT et al.: "Salvage of ischemic myocardium by ibuprofen during infarction in the conscious dog" & Am. J. Cardiol. 1980, 46(1), 74-82 * Abstract *	4	
X	CHEMICAL ABSTRACTS, Vol. 93, no. 21, November 24, 1980, page 53, ref. 197765c ./.		TECHNICAL FIELDS SEARCHED (Int. Cl. 7) C 07 C 57/00 A 61 K 31/00
INCOMPLETE SEARCH <p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 4</p> <p>Claims not searched: 1-3 Method for treatment of the</p> <p>Reason for the limitation of the search: human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention).</p>			
Place of search The Hague		Date of completion of the search 27-10-1982	Examiner KLAG
CATEGORY OF CITED DOCUMENTS <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>			



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PARTIAL EUROPEAN SEARCH REPORT

Application number:
EP 82 30 3756

-2-

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 1)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
P	<p>Columbus, Ohio, US W.C. WISE et al.: "Ibuprofen improves survival from endotoxic shock in the rat" & J. Pharmacol. Exp. Ther. 1980 215(1), 160-4</p> <p>* Abstract *</p> <p>--</p>	4	
	<p>CHEMICAL ABSTRACTS, Vol. 95, no. 17, October 26, 1981, page 39, ref. 144004p Columbus, Ohio, US T. UTSUNOMIYA et al.: "Treatment of aspiration pneumonia with ibuprofen and prostacyclin" & Surgery (St. Louis) 1981, 90(2) 170-6</p> <p>* Abstract *</p> <p>----</p>	4	<p>TECHNICAL FIELDS SEARCHED (Int. Cl. 3)</p>